Received: 16 March 2021 | Revised: 8 May 2021 | Accepted: 17 June 2021

DOI: 10.1002/cbin.11653

MINI-REVIEW

Cell Biology International WILEY

miRNAs; a novel strategy for the treatment of COVID-19

Hao Ying[1] | Mohsen Ebrahimi[2] | Mona Keivan[3] | Seyed Esmaeil Khoshnam[4] | Sarvenaz Salahi[5] | Maryam Farzaneh[3]

[1]Zhuji People's Hospital of Zhejiang Province, Zhuji Affiliated Hospital of Shaoxing University, Zhuji, China

[2]Neonatal and Children's Health Research Center, Golestan University of Medical Sciences, Gorgan, Iran

[3]Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[4]Persian Gulf Physiology Research Center, Medical Basic Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[5]Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran

Correspondence
Hao Ying, Zhuji People's Hospital of Zhejiang Province, Zhuji Affiliated Hospital of Shaoxing University, Zhuji 311800, China.
Email: yingyuhan2018@163.com

Maryam Farzaneh, Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Email: Maryamfarzaneh2013@yahoo.com

Abstract

Coronavirus disease 2019 (COVID-19) is the seventh member of the bat severe acute respiratory syndrome family. COVID-19 can fuse their envelopes with the host cell membranes and deliver their genetic material. COVID-19 attacks the respiratory system and stimulates the host inflammatory responses, enhances the recruitment of immune cells, and promotes angiotensin-converting enzyme 2 activities. Patients with confirmed COVID-19 may have experienced fever, dry cough, headache, dyspnea, acute kidney injury, acute respiratory distress syndrome, and acute heart injury. Several strategies such as oxygen therapy, ventilation, antibiotic or antiviral therapy, and renal replacement therapy are commonly used to decrease COVID-19-associated mortality. However, these approaches may not be good treatment options. Therefore, the search for an alternative-novel therapy is urgently important to prevent the disease progression. Recently, microRNAs (miRNAs) have emerged as a promising strategy for COVID-19. The design of oligonucleotide against the genetic material of COVID-19 might suppress virus RNA translation. Several previous studies have shown that host miRNAs play an antiviral role and improve the treatment of patients with COVID-19. miRNAs by binding to the 3′-untranslated region (UTR) or 5′-UTR of viral RNA play an important role in COVID-19-host interplay and viral replication. miRNAs interact with multiple pathways and reduce inflammatory biomarkers, thrombi formation, and tissue damage to accelerate the patient outcome. The information in this review provides a summary of the current clinical application of miRNAs for the treatments of patients with COVID-19.

KEYWORDS

ACE2, antiviral, coronavirus, COVID-19, miRNAs, viral RNA

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACI, acute cardiac injury; ADAM17, ADAM metallopeptidase domain 17; AKI, acute kidney injury; antimiR, antagonist miR; ARDS, acute respiratory distress syndrome; cc-miR, complete complementary miRNA; COVID-19, coronavirus disease 2019; CSF1 gene, colony-stimulating factor 1; EVs, extracellular vesicles; Exp5, exportin-5; GO, gene ontology; IL-1, interleukin-1; LncRNAs, long noncoding RNAs; miRNAs, microRNAs; mRNAs, messenger RNAs; Pre-miRNA, precursor miRNA; Pri-miRNAs, primary miRNAs; RISC, RNA-induced silencing complex; SARS, severe acute respiratory syndrome; TLR, Toll-Like receptors; TMPRSS2, Type II transmembrane serine proteases.; TNF, tumor necrosis factor; TRBP, transactivating response RNA-binding protein.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) for the first time emerged in Wuhan (the capital of central China's Hubei province) and later spread worldwide (Bernheim et al., 2020; Diao et al., 2020; Lauer et al., 2019). COVID-19 has been reported as the seventh member of the bat severe acute respiratory syndrome (SARS) family, which is known as SARS-CoV-2 (Lauer et al., 2019; Wang et al., 2020; Zhu et al., 2020). Coronaviruses are enveloped positive-sense RNA viruses that generally cause mild to acute respiratory infection in various species from bats to humans (Chang et al., 2020; Chen, 2020; Fung et al., 2020; Song, 2020). COVID-19 contains four structural proteins, including nucleocapsid (N) protein and membrane (M), spike (S), and small envelope (E) glycoproteins (Abu-Izneid et al., 2020). These viruses directly fuse to the plasma membrane, deliver their genetic materials, and complete their life cycle (Cascella et al., 2020; Jan & Arif, 2020). Initial symptoms for most patients with COVID-19 include fever, headache, shortness of breath, muscle soreness, sputum production, dyspnea, diarrhea, nausea, and fatigue (Bernheim et al., 2020; Huang et al., 2020; Jiang et al., 2020; Kui et al., 2020). A slight decrease in platelet levels and a massive release of tumor necrosis factor (TNF), plasminogen activators, and interleukin-1 and 6 (IL-1 and IL-6) have been reported to stimulate acute endothelial cell activation and microthrombus in lung vascularity (Schultz et al., 2021). COVID-19 infects the respiratory system, triggers widespread inflammation, promotes the recruitment of immune cells, and angiotensin-converting enzyme 2 (ACE2) activities (Abdi, 2020; Lauer et al., 2019). In a subset of high-risk patients (patients with diabetes or preexisting cardiovascular diseases or hypertension), acute cardiac injury, acute kidney injury, acute respiratory distress

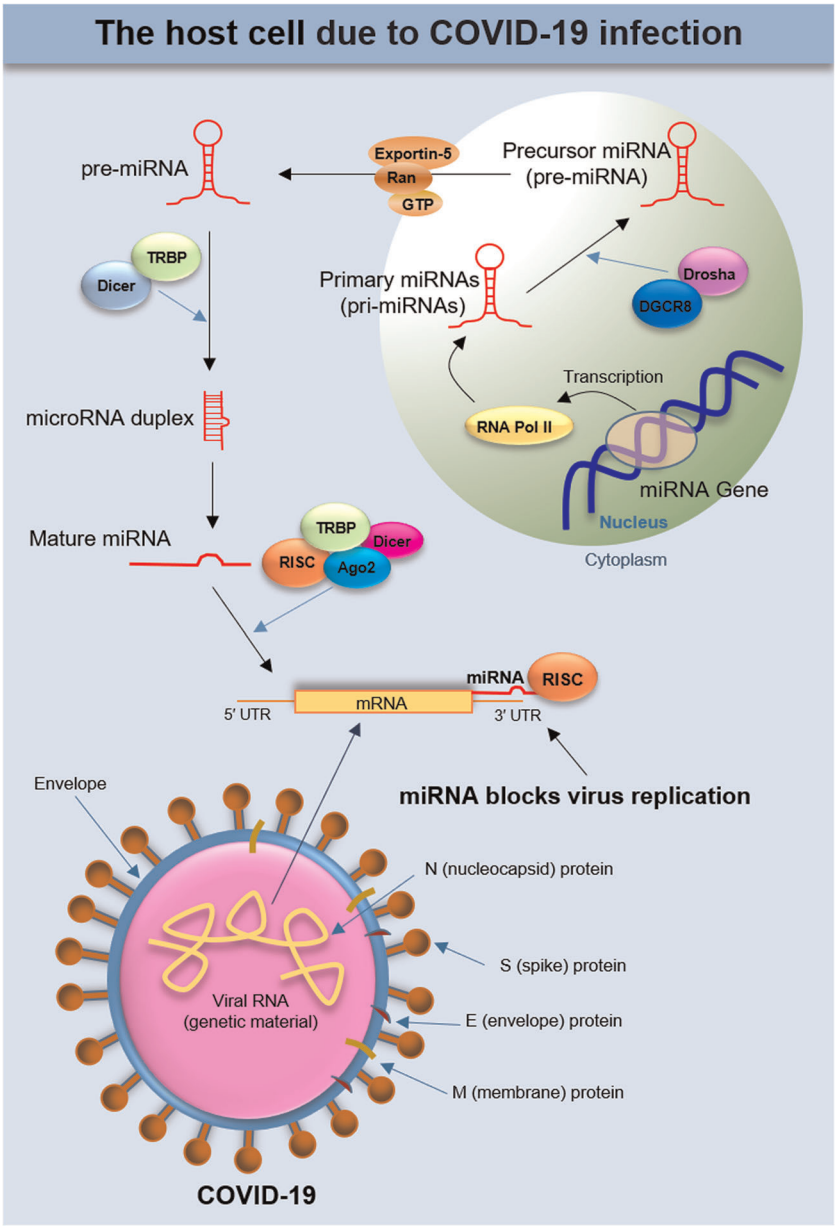

FIGURE 1 miRNA at cellular level due to COVID-19 infection. RNA polymerase II or III transcribed miRNA genes and generates pri-miRNAs (primary miRNAs). Subsequently, Drosha/DGCR8 holoenzyme (microprocessor cleavage) mediates processing of the pri-miRNA to generate the precursor miRNA (pre-miRNA) or a hairpin structured precursor (~60- to 70 nt) in the nucleus. The pre-miRNAs by Exportin-5 (Exp5) and Ran-GTP (a nucleocytoplasmic transporter) are delivered to the cytoplasm. The pre-miRNAs hairpin cleaved into a ~22 nucleotide duplex through Dicer (RNase III endonuclease) with the transactivating response RNA-binding protein (TRBP) to form a mature microRNA duplex. The mature miRNAs are created via RNA-induced silencing complex. miRNA binds with the AGO protein (RNA-induced silencing complex [RISC]) to target messenger RNA (mRNA) and trigger mRNA cleavage, mRNA degradation, and translation repression. COVID-19 contains four structural proteins, including nucleocapsid (N) protein and membrane (M), spike (S), and small envelope (E) glycoproteins. miRNAs by binding to the coding region or 5′-UTR of viral RNA play an important role in COVID-19-host interplay and viral replication. COVID-19, coronavirus disease 2019; miRNA, microRNA; UTR, untranslated region

syndrome (ARDS), and multiple organ dysfunction might be triggered (Chen et al., 2020; Huang et al., 2020; Xu et al., 2020).

Till now, various therapeutic modalities such as antibiotic therapy, antiviral therapy, glucocorticoids therapy, invasive and noninvasive ventilation, and renal replacement therapy have been assessed in clinical settings for COVID-19 patients (Chen et al., 2020; Chen et al., 2020; Heymann & Shindo, 2020; Huang et al., 2020; MacLaren et al., 2020; Wang et al., 2020; Zhou et al., 2020). However, these strategies are not likely to be safe and effective treatment options against COVID-19 (Jean et al., 2020; Momekov & Momekova, 2020). Therefore, the search for an alternative-novel therapy is urgently important to prevent the disease progression (Widiasta et al., 2020). Recently, microRNAs (miRNAs) have been emerged as antiviral regulators of viral genes (Gong & Zhang, 2020; Huang et al., 2021; Ramaiah, 2020). miRNAs through silencing genes play an important role in controlling the expression of transcription factors (Waheed & Zeng, 2020). Hence, it may be feasible to use miRNAs to overcome COVID-19 (El-Nabi et al., 2020; Mishra et al., 2020). miRNA-based therapeutic is a promising approach against heart failure or cardiovascular diseases, neurological disorders, tumorigenesis, and viral infection (Condrat et al., 2020; Cui et al., 2021; Takahashi et al., 2019). The design of oligonucleotide against the genetic material of COVID-19 might suppress virus RNA translation (Hassab Elnabi, 2020; Yu et al., 2020). Recent evidence suggests that miRNAs can improve the treatment of patients with COVID-19 (El-Nabi et al., 2020; Garg et al., 2021; Hassab Elnabi, 2020; Schultz et al., 2021). The information in this review provides a summary of the current clinical application of miRNAs for the treatments of patients with COVID-19.

2 | THE CANONICAL miRNA BIOGENESIS

miRNAs are a family of noncoding RNAs with an average of 22 nucleotides that interact with messenger RNAs (mRNAs) and play critical roles in controlling gene expression in a variety of biological processes (DeVeale et al., 2021). In most cases, miRNAs by miRNA-binding sites in the 3′-untranslated region (UTR) of the target mRNAs stimulate mRNA degradation and regulate posttranscriptional expression (Valinezhad Orang et al., 2014). Besides, miRNAs can bind with the 5′-UTR, gene promoters, and coding sequence (O'Brien et al., 2018).

RNA polymerase II or III transcribed miRNA genes and generates pri-miRNAs (primary miRNAs) (Borchert et al., 2006; Gregory et al., 2005). Subsequently, Drosha/DGCR8 holoenzyme (microprocessor cleavage) mediates processing of the pri-miRNA to generate the precursor miRNA (pre-miRNA) or a hairpin structured precursor (~60 to 70 nt) in the nucleus (Zeng et al., 2017). The pre-miRNAs by Exportin-5 (Exp5) and Ran-GTP (a nucleocytoplasmic transporter) are delivered to the cytoplasm (Wu et al., 2018). The pre-miRNAs hairpin cleaved into a ~22 nucleotide duplex through Dicer (RNase III endonuclease) with the transactivating response RNA-binding protein to form a mature miRNA duplex (Fareh et al., 2016; Graves & Zeng, 2012; Ha & Kim, 2014). The mature miRNAs are created via RNA-induced silencing complex (RISC) (Berezikov et al., 2007; Du & Zamore, 2005; Ruby et al., 2007). miRNA binds with the AGO protein (RISC) to target mRNA and trigger mRNA cleavage, mRNA degradation, and translation repression (Lam et al., 2015; Pu et al., 2019) (Figure 1). It is now accepted that the epigenetic modulation of miRNA expression plays an important role in several pathological processes after viral infections.

3 | THE POTENTIAL FUNCTION OF miRNAs FOLLOWING COVID-19 INFECTION

Growing evidence shows that the host-encoded miRNAs could modulate virus replication and pathogenesis (Khan et al., 2020; Tribolet et al., 2020; Wong et al., 2020; Zhang et al., 2020; Zheng et al., 2020). miRNAs through binding with viral RNA interact with different species or strain of viruses (Križnik et al., 2020; Trobaugh & Klimstra, 2017). miRNAs by binding to the 3′-UTR (El-Nabi et al., 2020; Liu et al., 2017) or 5′-UTR of viral RNA play an important role in COVID-19-host interplay and viral replication (Demirci & Adan, 2020; Nersisyan et al., 2020). miRNAs inhibited tissue damage and coagulation disturbs by suppressing coagulation cascade, cell death genes, and inflammatory agents in severe COVID-19 patients (Schultz et al., 2021).

Table 1 shows the most important miRNAs from the scientific literature that might act as good targets for COVID-19 drug development.

Schultz et al. (2021) revealed that the MSCs-derived extracellular vesicles could carry small and long noncoding RNAs and regulate the behavior of target cells. Their results showed that various miRNAs were associated with exacerbated cytokines and chemokines (258 miRNAs), cell death genes (266 miRNAs), and coagulation cascades (148 miRNAs) (Schultz et al., 2021). Based on their analysis, miR-125a-3p binds to the 3′-UTR region of TNF, CXCL10, IL2, IL7, IL10, IL15, and Factor XIII gene. miR-125a-3p reduces the systemic inflammation, coagulation disturbs, and cell death in severe COVID-19 patients. miR-125b-1-3p is another isoform that targets the 3′-UTR region of the TNF, interferon (IFN), CCL3, CXCL10, IL10, IL17A, IL18, IL33, Factor III, IX, XIII, and GSDME genes. miR-769-3p and miR-202-3p by targeting the 3′-UTR region of the TNF and IFN genes can decrease the cell death and tissue damage. In severe COVID-19 ICU patients, let-7e-5p by targeting the 3′-UTR region of the IL1A, IL1B, IL6R, IL10, IL15, TNF, RIPK1, CASP8, Factor VIII, and CSF3 genes could reduce the coagulation activation and cell death (Schultz et al., 2021).

Garg et al. (2021) evaluated changes in five circulating cardiovascular miRNAs, including miR-21 (fibrosis-associated miRNA), miR-126 (endothelial miRNA), miR-155 (cardiovascular disease and inflammation-associated miRNA), miR-208a (myocyte-associated miRNA), and miR-499 (myocyte-associated miRNA) in patients with mechanically-ventilated COVID-19. They found that serum concentration of four miRNAs such as miR-21, miR-155, miR-208a, and

TABLE 1 The most important miRNAs that might act as good targets for COVID-19 drug development

miRNAs	Target	Result	Ref.
miR-125a-3p	TNF, CXCL10, IL2, IL7, IL10, IL15, and Factor XIII	Reduces the systemic inflammation, coagulation disturbs, and cell death	(Schultz et al., 2021)
miR-125b-1-3p	TNF, IFN, CCL3, CXCL10, IL10, IL17A, IL18, IL33, Factor III, IX, XIII, and GSDME		
miR-769-3p	TNF and IFN	Decrease the cell death and tissue damage	
miR-202-3p			
let-7e-5p	IL1A, IL1B, IL6R, IL10, IL15, TNF, RIPK1, CASP8, Factor VIII, and CSF3	Reduces the coagulation activation and cell death	
miR-21	Myocardial/cardiomyocyte cells	Enhance endothelial cell dysfunction, inflammation, and myocardial damage	(Garg et al., 2021)
miR-155			
miR-208a			
miR-499			
miR-126	Endothelial cells	Protecting from endothelial damage	
has-miR-17-5p		Antiviral effect during host infection	(Khan et al., 2020)
has-miR-20b-5p			
hsa-miR323a-5p			
miR-18	ACE2	Kidney problems	(Widiasta et al., 2020)
miR-1207-5p	CSF1	Enhances macrophage recruitment and the acute inflammatory response	(Bertolazzi et al., 2020)
hsa-miR-588, hsa-miR-587, and hsa-miR-582-5p	ACE2	Enhance lung pathogenesis and injury	(Kim et al., 2020)
hsa-miR-221-3p and hsa-miR-95-5p	ADAM17		
hsa-miR-140-3p and hsa-miR-1255b	TMPRSS2		
miR-5197–3p, miR-4778-3p, and miR-6864-5p	The KEGG and GO pathways	Increases the pathogenicity	(Arisan et al., 2020)
miR-8066	The KEGG pathway, TGF-beta signaling, PRLR, CXCL6, IL6, IL17, and ACVR1 genes		
miR-5197-3p	Enhances the interaction of cc-miR2 with the gRNA	Decreases the pathogenicity	(Ivashchenko et al., 2020)
hsa-let-7a-g/i	TMPRSS2	Regulation of viral receptor and the host immunity	(Pontecorvi et al., 2020)
hsa-miR-98-5p	TMPRSS2		
hsa-miR-145	ADAM17		
hsa-miR-222	ADAM17		
hsa-miR-19a/b-3p	Furin		
hsa-miR-20b	Furin		
hsa-miR-106a	Furin		
hsa-miR-4661-3p	3′-UTR of the S gene	Inhibits the viral gene expression	(Liu et al., 2020)
MR147-3p	TMPRSS2	Enhances the gastrointestinal infection	

Abbreviations: ACE2, angiotensin-converting enzyme 2; ADAM17, ADAM metallopeptidase domain 17; cc-miR2, cc-miR for COVID-19; CSF1, colony-stimulating factor 1; GO, gene ontology; gRNA, mRNA of the COVID-19 genome; miRNA, microRNAs; TGF, transforming growth factor; TMPRSS2, Type II transmembrane serine proteases.

miR-499 were significantly increased in COVID-19 patients. Whereas serum concentration of miR-126 (protective from endothelial damage) was significantly reduced compared to healthy controls. According to previous studies, miR-21 and miR-126 participate in endothelial cell dysfunction, miR-155 stimulates inflammation, and miR-208a and miR-499 are associated with myocardial/cardiomyocyte damage (Garg et al., 2021; Hartmann et al., 2016). Hence, the upregulation of these miRNAs might be a predictor of inflammation and myocardial damage (Garg et al., 2021).

Khan et al. (2020) showed that three host miRNAs, including has-miR-17-5p, has-miR-20b-5p, and hsa-miR-323a-5p had an antiviral effect against COVID-19. They suggested that miRNAs may specifically inhibit several Toll-Like receptors pathways to modulate the host antiviral defense mechanism. Guterres et al. (2020) followed different stages of COVID-19 infection and found some miRNAs for positive-sense viral RNA (34 miRNA) and negative-sense (45 miRNAs) that target the key COVID-19 genes. Bertolazzi et al. (2020), reported that COVID-19 as an exogenous competing RNA could upregulate the expression of miR-1207-5p. In severe COVID-19, miR-1207-5p by targeting the CSF1 gene (colony-stimulating factor 1 or macrophage colony-stimulating factor) enhanced macrophage recruitment and the acute inflammatory response. Although decrease in ACE2 as a transmembrane protein is critical in ARDS pathogenesis (Imai et al., 2005), previous studies demonstrated that ACE2 is responsible for various indications of COVID-19 and kidney problems (Hardenberg & Luft, 2020; Perico et al., 2020). Widiasta et al. (2020) illustrated that miR-18 (miRNA in nephropathy) can regulate ACE2 expression following COVID-19 infection. Therefore, miR-18 may be a suitable target for the kidney pathogenesis of COVID-19 and ACE2 related diseases. Nersisyan et al. (2020) evaluated the interaction of six miRNAs, including miR-21-3p, miR-195-5p, miR-16-5p, miR-3065-5p, miR-424-5p, and miR-421 with human COVID-19 RNAs. They suggested that the expression of miR-21-3p was significantly increased in mouse lungs fallowing infection. Hosseini Rad and McLellan (2020) observed that the expression of miR-197-5p was upregulated in patients with cardiovascular disease. Therefore, these patients were more susceptible to COVID-19 infection. Arisan et al. (2020) illustrated that seven miRNAs, including miR-8066, miR-5197, miR-3611, miR-3934-3p, miR-1307-3p, miR-3691-3p, and miR-1468-5p by targeting the KEGG pathways increased viral pathogenicity and host responses. They found that miR-5197-3p, miR-4778-3p, and miR-6864-5p influenced on the gene ontology and KEGG pathways, and significantly promoted COVID-19 pathogenesis. They also reported that miR-8066 by targeting the KEGG pathway, TGF-beta signaling, PRLR, CXCL6, IL6, IL17, and ACVR1 genes increased the pathogenicity of COVID-19. So, these pathways may help to assess better therapeutic in COVID-19-infected patients.

Ivashchenko et al. (2020) found that synthetic miRNAs such as complete complementary miRNA (cc-miR as therapeutic agents can be used to inhibit the reproduction of the virus. They revealed that out of 2565 miRNAs, miR-4778-3p, miR-6864-5p and miR-5197-3p were the most effectively interacting with the gRNA of SARS-CoV, MERS-CoV, and COVID-19, respectively. miR-5197-3p enhanced the interaction of cc-miR2 (cc-miR for COVID-19, 25 nt) with the mRNA of the COVID-19 genome, without side effects on the host genome or competition with other sides.

Fulzele et al. (2020) assumed that some of the human miRNAs downregulated with aging which might affect COVID-19-host cell interaction and enhance severity and mortality among adult individuals more than 65 years with COVID-19. Kim et al. (2020) examined on hamster lung tissues infected by COVID-19 and showed that five miRNAs, including hsa-miR-15a-5p, hsa-miR-15b-5p, hsa-miR-195-5p, hsa-miR-16-5p, and hsa-miR-196a-1-3p could bind to COVID-19. Besides, seven miRNAs were found to bind to the ACE2 (hsa-miR-588, hsa-miR-587, and hsa-miR-582-5p), ADAM17 (ADAM metallopeptidase domain 17) (hsa-miR-221-3p and hsa-miR-95-5p), and type II transmembrane serine proteases (TMPRSS2) (hsa-miR-140-3p and hsa-miR-1255b) receptor proteins. They also found that levels of expression of five miRNAs, including hsa-miR-15b-5p, hsa-miR-195-5p, hsa-miR-221-3p, hsa-miR-140-3p, and hsa-miR-422a altered after infection. They suggested that hsa-miR-15b-5p and hsa-miR-195-5p may be suitable therapeutic biomarkers for COVID-19.

Mukhopadhyay et al. (2020) determined novel hypothalamic miRNAs that targeting to the ACE2 (31 miRNAs) and TMPRSS2 (29 miRNAs) genes. Therefore, these miRNAs via regulation of ACE2 and TMPRSS2 expression can be used to treat neurological symptoms in COVID-19 patients.

Li et al. (2020) evaluated the expression of miRNAs in the peripheral blood from patient with COVID-19. They found that the expression of some miRNAs was increased (35 miRNAs) or decreased (38 miRNAs). Besides, the expression of three miRNAs, including miR-183-5p, miR-627-5p, and miR-144-3p was significantly decreased. Pontecorvi et al. (2020) reported that the sex hormones in human host cells play important roles in COVID-19 lethality. They presented seven gender-associated miRNAs, including hsa-let-7a-g/i, hsa-miR-98-5p, hsa-miR-145, hsa-miR-222, hsa-miR-19a/b-3p, hsa-miR-20b, and hsa-miR-106a, which were localized on the X-chromosome and participated in regulation of COVID-19 receptors and host immunity. These miRNAs were reported to target the TMPRSS2, ADAM17, and Furin genes. Several hormones such as Estrogen/Erα, progesterone, androgen, Vitamin D, and 17β-Estradiol have been already identified that control the expression of these miRNAs.

Liu et al. predicted that hsa-miR-4661-3p could bind at the potential 3′-UTR of the S gene of COVID-19 and repressed the viral gene expression. In addition, MR147-3p as a virus-encoded miRNA increased the expression of TMPRSS2 and the gastrointestinal infection of COVID-19 (Liu et al., 2020). Therefore, miRNA can be a potent diagnostic biomarker for COVID-19 (Chauhan et al., 2020; Greco et al., 2020).

4 | LIMITATIONS OF miRNAs AGAINST COVID-19

miRNAs are an attractive therapeutic target that would facilitate the diagnosis and treatment of COVID-19 infection (Abu-Izneid et al., 2020; Canatan et al., 2020; Pierce et al., 2020). miRNAs as

potent epigenetic regulators stimulate the innate and adaptive immune system and influence the viral propagation (Mukhopadhyay & Mussa, 2020). However, different sets of miRNAs are expressed in the host system which target an entire immune pathway (Cho et al., 2020; Jia & Wei, 2020). Also, various miRNAs with multi-step maturation need several strategies to enhance miRNAs function and develop miRNAs-based therapeutics against COVID-19 (Abu-Izneid et al., 2020). Besides, manipulating endogenous miRNA to reduce the risk of COVID-19 infection may cause negative effects on the host genome (Ivashchenko et al., 2020; Mishra et al., 2020). Recently, the viral-encoded miRNAs have been shown to target several signaling pathways and critical cellular processes such as transcription, metabolism, and defense (Demirci & Adan, 2020; Mishra et al., 2020).

Demirci and Adan (2020) provided a list of miRNAs which involved in host-COVID-19 interaction. They assumed that the gonadotropin-releasing hormone receptor, Wnt, EGF, FGF, CCKR, and PDGF signaling pathways might be influenced by viral miRNA. Yu et al. (2020) used miRNA precursor prediction tools and identified location of three novel coronavirus miRNA precursors, including miR-P1-3p (first, second, and third). The COVID-19-encoded miRNAs as autocrine or paracrine agonists of host cells increased nuclear factor kappa B activity and stimulated proinflammatory cytokines (Arisan et al., 2020). Therefore, further investigation is required to identify specific miRNAs that target and stop virus-induced infection (Farshbaf et al., 2020; Pontecorvi et al., 2020).

5 | FUTURE STRATEGY USING miRNAs AGAINST COVID-19

Several previous studies identified the interactions between miRNA and SARS-CoV-2 and reported novel approaches against SARS-CoV-2 infection (Rizkita & Astuti, 2021). It has also been reported that antiviral miRNAs (miR-24, miR-124, and miR-744) by targeting the p38 MAPK pathway play an important role against respiratory virus infection (McCaskill et al., 2017). Although current strategies using miRNAs for treating COVID-19 are limited, potential binding sites on COVID-19 may highlight the roles of miRNAs in regulating COVID-19 infections (Alam & Lipovich, 2021; Hum et al., 2021). miRNAs have been shown to interact with the viral genome, affect vital processes, regulate the host's cellular microenvironment and the innate immune network (Demongeot & Seligmann, 2020; Hum et al., 2021). Recently, two approaches for miRNA-targeted therapy by the use of miRNA antagonists or inhibitors (Cobomarsen, an inhibitor of miR-155) (Seto et al., 2018) and miRNA mimics (Remlarsen, a miR-29 mimic) (Gallant-Behm et al., 2019) were found to support the efficient expression of proteins in the host and decrease the negative effects of miRNAs on the host cells (Gasparello et al., 2021). Miravirsen is a miR-122 antagonist and the first miRNA-based drug, which downregulates viral RNA levels (Santaris Pharma A/S, Phase II clinical trial) (Janssen et al., 2013; Okuyan & Begen, 2021). Therefore, antagonist miR (antimiR) and miR mimic could be innovative approach for the treatment of COVID-19 infections (Rizkita & Astuti, 2021). However, miRNA-COVID-19 interaction is a complex process that may enhance or suppress viral replication (El-Nabi et al., 2020; Fani et al., 2021).

Among the current efforts for the treatment of COVID-19, recent experiments developed animal models for COVID-19 to accelerate the preclinical testing of vaccines (Muñoz-Fontela et al., 2020). Corbett et al. (2020) assessed the mRNA-1273 vaccine against COVID-19 and showed rapid protection in the upper and lower airways in nonhuman primates. Despite the challenges of safe and effective vaccine manufacturing (Forman et al., 2021; Heaton, 2020), in the case of miRNA-COVID-19 interaction, further experimental is still required to generate miRNA-based animal models of COVID-19 to improve vaccine efficacy.

6 | CONCLUSION

COVID-19 infection stimulates inflammation and endothelial cell damage in multiorgans with cardiac injury (Garg et al., 2021). Viruses-derived miRNA can impact the host miRNA expression level and improve virus pathogenicity (Abu-Izneid et al., 2020). Host-derived miRNAs play essential roles in limiting viral replication (Barbu et al., 2020; Wong et al., 2020). There is evidence that miRNAs are able to downregulate the viral replication, modulate viral infectious progress, and enhance the survival rates in severe COVID-19 patients (Schultz et al., 2021). miRNAs interact with multiple pathways and reduce inflammatory biomarkers, thrombi formation, and tissue damage to accelerate the patient outcome (Schultz et al., 2021).

According to the literature, the interaction of host miRNA with the COVID-19-encoded mRNAs may alter by age, underlying chronic disease (diabetes, lung, and cardiovascular disorders), and gender. Also, the ACE2, TMPRSS2, and ADAM17 genes might serve as potent targets in patients with COVID-19. However, more investigations are needed to confirm their interactions with miRNAs in COVID-19 and in other infectious events.

CONFLICT OF INTERESTS

None of the authors have any conflict of interest.

AUTHOR CONTRIBUTIONS

Hao Ying, Mohsen Ebrahimi, and Maryam Farzaneh have been involved in drafting the manuscript. Mona Keivan, and Seyed Esmaeil Khoshnam have made substantial contributions to the revising of the manuscript and the design of the Table. Sarvenaz Salahi has made a substantial contribution to the writing and the design of the Figure. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

There is no data availability statement.

ORCID

Maryam Farzaneh http://orcid.org/0000-0001-6239-8745

REFERENCES

Abdi, M. (2020). Coronavirus disease 2019 (COVID-19) outbreak in Iran; actions and problems. *Infection Control & Hospital Epidemiology*, *41*(6), 754–755.

Abu-Izneid, T., AlHajri, N., Ibrahim, A. M., Javed, M. N., Salem, K. M., Pottoo, F. H., & Kamal, M. A. (2020). Micro-RNAs in the regulation of immune response against SARS CoV-2 and other viral infections. *Journal of Advanced Research*, *30*, 133–145.

Alam, T., & Lipovich, L. (2021). miRCOVID-19: Potential targets of human miRNAs in SARS-CoV-2 for RNA-based drug discovery. *Non-coding RNA*, *7*, 18.

Arisan, E. D., Dart, A., Grant, G. H., Arisan, S., Cuhadaroglu, S., Lange, S., & Uysal-Onganer, P. (2020). The prediction of miRNAs in SARS-CoV-2 genomes: hsa-miR databases identify 7 key miRs linked to host responses and virus pathogenicity-related KEGG pathways significant for comorbidities. *Viruses*, *12*, 614.

Barbu, M. G., Condrat, C. E., Thompson, D. C., Bugnar, O. L., Cretoiu, D., Toader, O. D., Suciu, N., & Voinea, S. C. (2020). MicroRNA involvement in signaling pathways during viral infection. *Frontiers in Cell and Developmental Biology*, *8*, 143.

Berezikov, E., Chung, W.-J., Willis, J., Cuppen, E., & Lai, E. C. (2007). Mammalian mirtron genes. *Molecular Cell*, *28*, 328–336.

Bernheim, A., Mei, X., Huang, M., Yang, Y., Fayad, Z. A., Zhang, N., Diao, K., Lin, B., Zhu, X., Li, K., & Chest, C. T. (2020). Findings in coronavirus disease-19 (COVID-19): Relationship to duration of infection. *Radiology*, 200463.

Bertolazzi, G., Cipollina, C., Benos, P. V., Tumminello, M., & Coronnello, C. (2020). miR-1207-5p can contribute to dysregulation of inflammatory response in COVID-19 via targeting SARS-CoV-2 RNA. *Frontiers in Cellular and Infection Microbiology*, *10*, 586592.

Borchert, G. M., Lanier, W., & Davidson, B. L. (2006). RNA polymerase III transcribes human microRNAs. *Nature Structural & Molecular Biology*, *13*, 1097–1101.

Canatan, D., De, & Sanctis, V. (2020). The impact of MicroRNAs (miRNAs) on the genotype of coronaviruses. *Acta Bio-Medica: Atenei Parmensis*, *91*, 195–198.

Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S. C., & Di Napoli, R. (2020). Features, evaluation and treatment coronavirus (COVID-19), in: StatPearls [Internet], StatPearls Publishing.

Chang, L., Yan, Y., & Wang, L. (2020). Coronavirus disease 2019: Coronaviruses and blood safety. *Transfusion Medicine Reviews*, *34*(2), 75–80.

Chauhan, N., Jaggi, M., Chauhan, S. C., & Yallapu, M. M. (2020). COVID-19: Fighting the invisible enemy with microRNAs. *Expert Review of Anti-Infective Therapy*, *19*(2), 137–145.

Chen, J. (2020). Pathogenicity and transmissibility of 2019-nCoV—a quick overview and comparison with other emerging viruses. *Microbes and Infection*, *22*(2), 69–71.

Chen, L., Liu, H., Liu, W., Liu, J., Liu, K., Shang, J., Deng, Y., & Wei, S. (2020). Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Zhonghua jie he he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases*, *43*, E005.

Cho, S., Tai, J. W., & Lu, L.-F. (2020). MicroRNAs and their targetomes in tumor-immune communication. *Cancers*, *12*, 2025.

Condrat, C. E., Thompson, D. C., Barbu, M. G., Bugnar, O. L., Boboc, A., Cretoiu, D., Suciu, N., Cretoiu, S. M., & Voinea, S. C. (2020). miRNAs as biomarkers in disease: Latest findings regarding their role in diagnosis and prognosis. *Cells*, *9*, 276.

Corbett, K. S., Flynn, B., Foulds, K. E., Francica, J. R., Boyoglu-Barnum, S., Werner, A. P., Flach, B., O'Connell, S., Bock, K. W., Minai, M., Nagata, B. M., Andersen, H., Martinez, D. R., Noe, A. T., Douek, N., Donaldson, M. M., Nji, N. N., Alvarado, G. S., Edwards, D. K., … Graham, B. S. (2020). Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. *New England Journal of Medicine*, *383*, 1544–1555.

Cui, Y., Wan, H., & Zhang, X. (2021). MiRNA in food simultaneously controls animal viral disease and human tumorigenesis. *Molecular Therapy-Nucleic Acids*, *23*, 995–1006.

Demirci, M. D. S., & Adan, A. (2020). Computational analysis of microRNA-mediated interactions in SARS-CoV-2 infection. *PeerJ*, *8*, e9369.

Demongeot, J., & Seligmann, H. (2020). SARS-CoV-2 and miRNA-like inhibition power. *Medical Hypotheses*, *144*, 110245.

DeVeale, B., Swindlehurst-Chan, J., & Blelloch, R. (2021). The roles of microRNAs in mouse development. *Nature Reviews Genetics*, *22*, 307–323.

Diao, M., Zhang, S., Chen, D., & Hu, W. (2020). The novel coronavirus (COVID-19) infection in Hangzhou: An experience to share. *Infection Control & Hospital Epidemiology*, *41*(7), 874–875.

Du, T., & Zamore, P. D. (2005). microPrimer: The biogenesis and function of microRNA. *Development*, *132*, 4645–4652.

El-Nabi, S. H., Elhiti, M., & El-Sheekh, M. (2020). A new approach for COVID-19 treatment by micro-RNA. *Medical Hypotheses*, *143*, 110203.

Fani, M., Zandi, M., Ebrahimi, S., Soltani, S., & Abbasi, S. (2021). The role of miRNAs in COVID-19 disease. *Future Virology*, *16*(4), 301–306.

Fareh, M., Yeom, K.-H., Haagsma, A. C., Chauhan, S., Heo, I., & Joo, C. (2016). TRBP ensures efficient Dicer processing of precursor microRNA in RNA-crowded environments. Nature. *Communications*, *7*, 13694.

Farshbaf, A., Mohtasham, N., Zare, R., Mohajertehran, F., & Rezaee, S. A. (2020). Potential therapeutic approaches of microRNAs for COVID-19: Challenges and opportunities. *Journal of oral biology and craniofacial research*, *11*(2), 132–137.

Forman, R., Shah, S., Jeurissen, P., Jit, M., & Mossialos, E. (2021). COVID-19 vaccine challenges: What have we learned so far and what remains to be done? *Health Policy*, *125*, 553–567.

Fulzele, S., Sahay, B., Yusufu, I., Lee, T. J., Sharma, A., Kolhe, R., & Isales, C. M. (2020). COVID-19 virulence in aged patients might be impacted by the host cellular MicroRNAs abundance/profile. *Aging and Disease*, *11*, 509–522.

Fung, S.-Y., Yuen, K.-S., Ye, Z.-W., Chan, C.-P., & Jin, D.-Y. (2020). A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: Lessons from other pathogenic viruses. *Emerging Microbes & Infections*, *9*, 558–570.

Gallant-Behm, C. L., Piper, J., Lynch, J. M., Seto, A. G., Hong, S. J., Mustoe, T. A., Maari, C., Pestano, L. A., Dalby, C. M., & Jackson, A. L. (2019). A microRNA-29 mimic (remlarsen) represses extracellular matrix expression and fibroplasia in the skin. *Journal of Investigative Dermatology*, *139*, 1073–1081.

Garg, A., Seeliger, B., Derda, A. A., Xiao, K., Gietz, A., Scherf, K., Sonnenschein, K., Pink, I., Hoeper, M. M., Welte, T., Bauersachs, J., David, S., Bär, C., & Thum, T. (2021). Circulating cardiovascular microRNAs in critically ill COVID-19 patients Short title: MicroRNA signatures in COVID-19. *European Journal of Heart Failure*, *23*(3), 468–475.

Gasparello, J., Finotti, A., & Gambari, R. (2021). Tackling the COVID-19 "cytokine storm" with microRNA mimics directly targeting the 3'UTR of pro-inflammatory mRNAs. *Medical Hypotheses*, *146*, 110415.

Gong, Y., & Zhang, X. (2020). RNAi-based antiviral immunity of shrimp. *Developmental & Comparative Immunology*, *115*, 103907.

Graves, P., & Zeng, Y. (2012). Biogenesis of mammalian microRNAs: A global view. *Genomics, Proteomics & Bioinformatics*, *10*, 239–245.

Greco, S., Madè, A., Gaetano, C., Devaux, Y., Emanueli, C., & Martelli, F. (2020). Noncoding RNAs implication in cardiovascular diseases in the COVID-19 era. *Journal of Translational Medicine*, *18*, 408.

Gregory, R. I., Chendrimada, T. P., Cooch, N., & Shiekhattar, R. (2005). Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. *Cell*, *123*, 631–640.

Guterres, A., de Azeredo Lima, C. H., Miranda, R. L., & Gadelha, M. R. (2020). What is the potential function of microRNAs as biomarkers and therapeutic targets in COVID-19? *Infection, Genetics and Evolution*, *85*, 104417.

Ha, M., & Kim, V. N. (2014). Regulation of microRNA biogenesis. *Nature Reviews Molecular Cell Biology*, *15*, 509–524.

Hardenberg, J.-H. B., & Luft, F. C. (2020). Covid-19, ACE2 and the kidney. *Acta physiologica (Oxford, England)*, *230*, e13539–e13539.

Hartmann, D., Fiedler, J., Sonnenschein, K., Just, A., Pfanne, A., Zimmer, K., Remke, J., Foinquinos, A., Butzlaff, M., & Schimmel, K. (2016). MicroRNA-based therapy of GATA2-deficient vascular disease. *Circulation*, *134*, 1973–1990.

Hassab Elnabi, S. E. (2020). New strategies for treatment of COVID-19 and evolution of SARS-CoV-2 according to biodiversity and evolution theory. *Egyptian Journal of Basic and Applied Sciences*, *7*, 226–232.

Heaton, P. M. (2020). Challenges of developing novel vaccines with particular global health importance. *Frontiers in immunology*, *11*, 517290.

Heymann, D. L., & Shindo, N. (2020). COVID-19: What is next for public health? *The Lancet*, *395*(10224), 542–545.

Hosseini Rad, S. M. A., & McLellan, A. D. (2020). Implications of SARS-CoV-2 mutations for genomic RNA structure and host microRNA targeting. *International Journal of Molecular Sciences*, *21*, 4807.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., & Gu, X. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*, 497–506.

Huang, J.-H., Han, T.-T., Li, L.-X., Qu, T., Zhang, X.-Y., Liao, X., & Zhong, Y. (2021). Host microRNAs regulate expression of hepatitis B virus genes during transmission from patients' sperm to embryo. *Reproductive Toxicology*, *100*, 1–6.

Hum, C., Loiselle, J., Ahmed, N., Shaw, T. A., Toudic, C., & Pezacki, J. P. (2021). MicroRNA mimics or inhibitors as antiviral therapeutic approaches against COVID-19. *Drugs*, *81*, 517–531.

Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., Yang, P., Sarao, R., Wada, T., Leong-Poi, H., Crackower, M. A., Fukamizu, A., Hui, C.-C., Hein, L., Uhlig, S., Slutsky, A. S., Jiang, C., & Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*, *436*, 112–116.

Ivashchenko, A., Rakhmetullina, A., & Aisina, D. (2020). How miRNAs can protect humans from coronaviruses COVID-19. *SARS-CoV, and MERS-CoV*.

Jan, R. A., & Arif, S. (2020). Another coronavirus, Another challenge. JMS SKIMS, 23.

Janssen, H. L., Reesink, H. W., Lawitz, E. J., Zeuzem, S., Rodriguez-Torres, M., Patel, K., Van Der Meer, A. J., Patick, A. K., Chen, A., & Zhou, Y. (2013). Treatment of HCV infection by targeting microRNA. *New England Journal of Medicine*, *368*, 1685–1694.

Jean, S.-S., Lee, P.-I., & Hsueh, P.-R. (2020). Treatment options for COVID-19: The reality and challenges. *Journal of Microbiology, Immunology and Infection*, *53*, 436–443.

Jia, Y., & Wei, Y. (2020). Modulators of MicroRNA Function in the Immune System. *International Journal of Molecular Sciences*, *21*, 2357.

Jiang, F., Deng, L., Zhang, L., Cai, Y., Cheung, C. W., & Xia, Z. (2020). Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *Journal of General Internal Medicine*, *35*, 1545–1549.

Khan, M. A.-A.-K., Sany, M. R. U., Islam, M. S., & Islam, A. B. M. M. K. (2020). Epigenetic regulator miRNA pattern differences among SARS-CoV, SARS-CoV-2, and SARS-CoV-2 world-wide isolates delineated the mystery behind the epic pathogenicity and distinct clinical characteristics of pandemic COVID-19. *Frontiers in Genetics*, *11*, 765.

Kim, W. R., Park, E. G., Kang, K. W., Lee, S. M., Kim, B., & Kim, H. S. (2020). Expression analyses of microRNAs in Hamster lung tissues infected by SARS-CoV-2. *Molecules and Cells*, *43*, 953–963.

Križnik, M., Baebler, Š., & Gruden, K. (2020). Roles of small RNAs in the establishment of tolerant interaction between plants and viruses. *Current Opinion in Virology*, *42*, 25–31.

Kui, L., Fang, Y.-Y., Deng, Y., Liu, W., Wang, M.-F., Ma, J.-P., Xiao, W., Wang, Y.-N., Zhong, M.-H., & Li, C.-H. (2020). Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chinese Medical Journal*, *133*(9), 1025–1031.

Lam, J. K. W., Chow, M. Y. T., Zhang, Y., & Leung, S. W. S. (2015). siRNA Versus miRNA as therapeutics for gene silencing. *Molecular Therapy Nucleic Acids*, *4*, e252.

Lauer, S. A., Grantz, K. H., Bi, Q., Jones, F. K., Zheng, Q., Meredith, H. R., Azman, A. S., Reich, N. G., & Lessler, J.The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Annals of Internal Medicine.

Li, C., Hu, X., Li, L., & Li, J. H. (2020). Differential microRNA expression in the peripheral blood from human patients with COVID-19. *Journal of Clinical Laboratory Analysis*, *34*, e23590.

Liu, Q., Du, J., Yu, X., Xu, J., Huang, F., Li, X., Zhang, C., Li, X., Chang, J., Shang, D., Zhao, Y., Tian, M., Lu, H., Xu, J., Li, C., Zhu, H., Jin, N., & Jiang, C. (2017). miRNA-200c-3p is crucial in acute respiratory distress syndrome. *Cell Discovery*, *3*, 17021.

Liu, Z., Wang, J., Xu, Y., Guo, M., Mi, K., Xu, R., Pei, Y., Zhang, Q., Luan, X., & Hu, Z., Implications of the virus-encoded miRNA and host miRNA in the pathogenicity of SARS-CoV-2. arXiv preprint arXiv:2004.04874 2020.

MacLaren, G., Fisher, D., & Brodie, D., Preparing for the Most Critically Ill Patients With COVID-19: The Potential Role of Extracorporeal Membrane Oxygenation. JAMA 2020.

McCaskill, J. L., Ressel, S., Alber, A., Redford, J., Power, U. F., Schwarze, J., Dutia, B. M., & Buck, A. H. (2017). Broad-spectrum inhibition of respiratory virus infection by microRNA mimics targeting p38 MAPK signaling. *Molecular Therapy-Nucleic Acids*, *7*, 256–266.

Mishra, R., Kumar, A., Ingle, H., & Kumar, H. (2020). The interplay between viral-derived miRNAs and host immunity during infection. *Frontiers in immunology*, *10*, 3079.

Momekov, G., & Momekova, D. (2020). Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: Antiviral levels are not likely attainable with known dosing regimens. *Biotechnology & Biotechnological Equipment*, *34*, 469–474.

Mukhopadhyay, D., & Mussa, B. M. (2020). Identification of novel hypothalamic microRNAs as promising therapeutics for SARS-CoV-2 by regulating ACE2 and TMPRSS2 expression: An in silico analysis. *Brain Sciences*, *10*, 666.

Muñoz-Fontela, C., Dowling, W. E., Funnell, S. G. P., Gsell, P.-S., Riveros-Balta, A. X., Albrecht, R. A., Andersen, H., Baric, R. S., Carroll, M. W., Cavaleri, M., Qin, C., Crozier, I., Dallmeier, K., de Waal, L., de Wit, E., Delang, L., Dohm, E., Duprex, W. P., Falzarano, D., … Barouch, D. H. (2020). Animal models for COVID-19. *Nature*, *586*, 509–515.

Nersisyan, S., Engibaryan, N., Gorbonos, A., Kirdey, K., Makhonin, A., & Tonevitsky, A. (2020). Potential role of cellular miRNAs in coronavirus-host interplay. *PeerJ*, *8*, e9994.

O'Brien, J., Hayder, H., Zayed, Y., & Peng, C. (2018). Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Frontiers in. Endocrinology, *9*.

Okuyan, H. M., & Begen, M. A. (2021). miRNAs as attractive diagnostic and therapeutic targets for Familial Mediterranean Fever. *Modern Rheumatology*, *32*(5), 1–25.

Perico, L., Benigni, A., & Remuzzi, G. (2020). Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade. *Nephron*, *144*, 213–221.

Pierce, J. B., Simion, V., Icli, B., Pérez-Cremades, D., Cheng, H. S., & Feinberg, M. W. (2020). Computational Analysis of Targeting SARS-CoV-2, Viral Entry Proteins ACE2 and TMPRSS2, and Interferon Genes by Host MicroRNAs, Genes (Basel) (p. 11).

Pontecorvi, G., Bellenghi, M., Ortona, E., & Carè, A., microRNAs as new possible actors in gender disparities of Covid-19 pandemic, in, Wiley Online Library, 2020.

Pu, M., Chen, J., Tao, Z., Miao, L., Qi, X., Wang, Y., & Ren, J. (2019). Regulatory network of miRNA on its target: Coordination between transcriptional and post-transcriptional regulation of gene expression. *Cellular and Molecular Life Sciences*, *76*, 441–451.

Ramaiah, M. J. (2020). mTOR inhibition and p53 activation, microRNAs: The possible therapy against pandemic COVID-19. *Gene Reports*, *20*, 100765.

Rizkita, L. D., & Astuti, I. (2021). The potential of miRNA-based therapeutics in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A review. *Journal of Pharmaceutical Analysis 11*(3), 1–9.

Ruby, J. G., Jan, C. H., & Bartel, D. P. (2007). Intronic microRNA precursors that bypass Drosha processing. *Nature*, *448*, 83.

Schultz, I. C., Bertoni, A. P. S., & Wink, M. R. (2021). Mesenchymal stem cell-derived extracellular vesicles carrying miRNA as a potential multi target therapy to COVID-19: An in silico analysis. *Stem Cell Reviews and Reports*, *17*(2), 341–356.

Seto, A. G., Beatty, X., Lynch, J. M., Hermreck, M., Tetzlaff, M., Duvic, M., & Jackson, A. L. (2018). Cobomarsen, an oligonucleotide inhibitor of miR-155, co-ordinately regulates multiple survival pathways to reduce cellular proliferation and survival in cutaneous T-cell lymphoma. *British Journal of Haematology*, *183*, 428–444.

Song, J., 2019-nCoV 3C-Like Protease carries an activity-enhancing T285/A variation which may contribute to its high infectivity. 2020.

Takahashi, R.-U., Prieto-Vila, M., Kohama, I., & Ochiya, T. (2019). Development of miRNA-based therapeutic approaches for cancer patients. *Cancer Prevention Research*, *110*, 1140–1147.

Tribolet, L., Kerr, E., Cowled, C., Bean, A. G., Stewart, C. R., Dearnley, M., & Farr, R. J. (2020). MicroRNA biomarkers for infectious diseases: From basic research to biosensing. *Frontiers in Microbiology*, 11.

Trobaugh, D. W., & Klimstra, W. B. (2017). MicroRNA regulation of RNA virus replication and pathogenesis. *Trends in Molecular Medicine*, *23*, 80–93.

Valinezhad Orang, A., Safaralizadeh, R., & Kazemzadeh-Bavili, M. (2014). Mechanisms of miRNA-mediated gene regulation from common downregulation to mRNA-specific upregulation. *International Journal of Genomics*, *2014*, 970607.

Waheed, S., & Zeng, L. (2020). The critical role of miRNAs in regulation of flowering time and flower development. *Genes*, *11*, 319.

Wang, C., Horby, P. W., Hayden, F. G., & Gao, G. F. (2020). A novel coronavirus outbreak of global health concern. *The Lancet*, *395*, 470–473.

Widiasta, A., Sribudiani, Y., Nugrahapraja, H., Hilmanto, D., Sekarwana, N., & Rachmadi, D. (2020). Potential role of ACE2-related microRNAs in COVID-19-associated nephropathy. *Non-coding RNA Research*, *5*, 153–166.

Wong, R. R., Abd-Aziz, N., Affendi, S., & Poh, C. L. (2020). Role of microRNAs in antiviral responses to dengue infection. *Journal of Biomedical Science*, *27*, 1–11.

Wu, K., He, J., Pu, W., & Peng, Y. (2018). The role of exportin-5 in microRNA biogenesis and cancer. *Genomics, Proteomics & Bioinformatics*, *16*, 120–126.

Xu, X.-W., Wu, X.-X., Jiang, X.-G., Xu, K.-J., Ying, L.-J., Ma, C.-L., Li, S.-B., Wang, H.-Y., Zhang, S., & Gao, H.-N. (2020). Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. *BMJ (London)*, *368*, 368.

Yu, T.-Y., Chen, M., & Wang, C.-D. (2020). Annotation of miRNAs in COVID-19 coronavirus. *Journal of Electronic Science and Technology*, *19*, 100060.

Zeng, C., Xia, J., Chen, X., Zhou, Y., Peng, M., & Zhang, W. (2017). MicroRNA-like RNAs from the same miRNA precursors play a role in cassava chilling responses. *Scientific Reports*, *7*, 17135.

Zhang, L., Yu, J., & Liu, Z. (2020). MicroRNAs expressed by human cytomegalovirus. *Virology Journal*, *17*, 1–12.

Zheng, B., Zhou, J., & Wang, H. (2020). Host microRNAs and exosomes that modulate influenza virus infection. *Virus Research*, *279*, 197885.

Zhou, Z.-G., Xie, S.-M., Zhang, J., Zheng, F., Jiang, D.-X., Li, K.-Y., Zuo, Q., Yan, Y.-S., Liu, J.-Y., & Xie, Y.-L., Short-Term Moderate-Dose Corticosteroid Plus Immunoglobulin Effectively Reverses COVID-19 Patients Who Have Failed Low-Dose Therapy. 2020.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., China Novel Coronavirus, I., & Research, T. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*, *382*, 727–733.

How to cite this article: Ying, H., Ebrahimi, M., Keivan, M., Khoshnam, S. E., Salahi, S., & Farzaneh, M. (2021). miRNAs; a novel strategy for the treatment of COVID-19. *Cell Biology International*, 1–9. https://doi.org/10.1002/cbin.11653